Acute Effects of Passive Smoking on Lung Function and Airway Reactivity in Asthmatic Subjects*

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We studied the acute effects of one hour of passive cigarette smoking on the lung function and airway reactivity of nine young adult asthmatic volunteers. At the time of this study, the subjects were asymptomatic and had normal or nearly normal lung function. Passive smoking produced no change in expiratory flow rates. However, there was a small *decrease* in nonspecific bronchial reactivity, as assessed by methacholine inhalation challenge testing ($p = 0.022$). Pharmacologically active substances present in cigarette smoke, such as nicotine, may explain the observed change in airway reactivity. Although the finding of decreased airway reactivity might suggest that passive smoking produces a "protective" effect on the underlying asthma, the observed change in reactivity was slight and of uncertain clinical significance. We conclude that passive smoking presents no acute respiratory risk to young asymptomatic asthmatic patients.

Nonsmokers are frequently exposed to tobacco smoke in indoor environments. The potential health risks of such involuntary, or passive, smoking is a topic of intense interest.[1,2] Current evidence suggests that passive smoking acutely lowers the angina threshold[3] and that chronic passive smoking may lead to small airways dysfunction[4] or lung cancer.[5] There is a paucity of data on whether asthmatics may be at special respiratory risk from passive smoking.

Asthma is characterized by hyperreactivity of the airways, such that a wide variety of different stimuli may cause bronchospasm and reduced airflow. Even if lung function tests are normal, bronchial hyperreactivity can be detected by bronchoprovocation challenge testing with inhaled agents such as histamine or methacholine.[6-12] In addition, bronchoprovocation testing may be useful for detecting changes in airway reactivity that occur in response to therapeutic interventions or environmental exposures. For example, such studies have demonstrated temporary increases in bronchial responsiveness following viral infections,[13] and antigen inhalation,[14] as well as exposure to ozone[15,16] and nitrogen dioxide.[17] Changes in nonspecific bronchial responsiveness may be clinically important since many studies have shown a correlation of airway reactivity with the clinical severity of asthma as determined by symptom scores, medication requirements, or dose of specific allergen required to produce airflow obstruction.[6-7,9,18]

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Two previous studies which examined the acute effects of passive smoking on lung function in asthmatics report conflicting results.[19,20] Furthermore, there is no published information concerning the effect of passive smoking on nonspecific airway responsiveness in asthmatics. Therefore, we investigated the effect of acute passive smoking on both lung function and airway reactivity in a group of young stable asthmatic patients.

Subjects and Methods

Nine asthmatic individuals ranging in age from 19 to 30 years were studied. Five subjects were males, and four were females. Subjects were selected from 11 consecutive respondents to an advertisement announcing the study. The diagnosis of asthma was made previously by the individual's physician. Respondents were included only if they were currently clinically stable and off oral asthma medications. Four individuals intermittently using inhaled bronchodilators at the time of the study were included. No subject with an upper respiratory infection within the preceding eight weeks was studied. Although the subjects were asymptomatic at the time of this study, five had required hospitalization for asthma in the past. However, no subject had been hospitalized for asthma within the preceding year. All individuals were nonsmokers. Individuals were not selected based upon a history of how they reacted in the presence of tobacco smoke. However, six of the subjects indicated that exposure to cigarette smoke "bothered" their asthma.

Subjects were instructed to avoid coffee, cola drinks, chocolate, and exercise for at least six hours before bronchoprovocation testing. No subject was taking vitamin C supplements. Subjects using an inhaled bronchodilator were instructed to withhold use for six to eight hours preceding the test, in accordance with published guidelines.[21] Before participation in the study, subjects signed a

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Table 1—*Protocol*

Day 1	Day 2
I. *Baseline studies* a. Spirometry (FEV_1, FVC, $\dot{V}max50$) b. Methacholine inhalation challenge	I. *Before passive smoking* a. Venous COHb analysis b. Spirometry II. *One hour smoke exposure* III. *After passive smoking* a. Venous COHb analysis b. Spirometry c. Methacholine inhalation challenge

consent form approved by the Yale Human Investigation Committee.

The experimental protocol was carried out in each subject on two separate days (Table 1). This design was utilized in order to avoid the need to do two methacholine challenges on the same day.[4] On the first day, baseline spirometry was measured with a pneumotachygraph-integrated flow-volume device[5] connected to a Gould 3054 high performance X-Y recorder. The forced vital capacity (FVC), the forced expiratory volume in one second (FEV_1), and the maximal expiratory flow rate at 50 percent of the vital capacity ($\dot{V}max50$) were determined. Following this, a methacholine inhalation challenged test was performed. The challenge test was conducted by delivering sequential doses of methacholine in phenol-buffered saline solution (0.05, 0.5, 1.0, 2.0, 5.0, 10.0, 25.0 mg/ml) via mouthpiece with a DeVilbiss No. 45 nebulizer. A noseclip was used. Each dose was delivered during two minutes of normal tidal breathing. The FEV_1 was determined at 0.5 and four minutes after each dose. If at either time there was a 20 percent or greater fall in FEV_1 from the baseline prechallenge value, the test was terminated. If the FEV_1 did not decrease by this amount, then the next dose was delivered. The cumulative dose of methacholine which corresponded to a 20 percent decrease in FEV_1 was determined by linear interpolation of the last two points on the dose-response curve.[6] This "provocative dose" of methacholine which causes a 20 percent decrease in FEV_1 is the $PD_{20}FEV_1$. A low $PD_{20}FEV_1$ indicates a high degree of nonspecific bronchial responsiveness.

On the second experiment day (24 to 48 hours following the first day), subjects returned for spirometry and then a baseline pre-smoke exposure venous blood sample was drawn for carboxyhemoglobin (COHb) analysis. The blood COHb level analysis was performed with a double-wavelength spectrophotometer.[7] The subject then entered a 4.25 m^3 environmental chamber for exposure to machine-generated cigarette smoke for one hour. Both sidestream and mainstream smoke filled the chamber. The same brand of a leading nonfilter cigarette was used in all experiments. The chamber was maintained at a temperature of about 25°C and the relative humidity was approximately 50 percent. Air turnover in the chamber was adjusted as necessary to maintain a carbon monoxide level in the ambient air of between 40 and 50 ppm. The carbon monoxide level was sampled continuously from an area near the subject. While in the chamber, the subjects were given the option to wear goggles to reduce eye irritation. These goggles did not cover the nose or mouth.

Immediately following one hour of passive smoking, the subject exited from the chamber and a venous blood sample was drawn for COHb analysis. Spirometric testing was performed, followed by a methacholine bronchoprovocation challenge. The chest of each subject was auscultated immediately before and after the passive smoke exposure.

A methacholine challenge test was also administered to 14 individuals (age 18 to 37 years, mean 28 years) who had normal pulmonary function test results and no history of asthma. The purpose was to compare the methacholine responsiveness of this "normal" group with that of the study population which had been selected based upon a prior history of asthma. The normal individuals did not participate in the passive smoking experiment.

Table 2—*Individual Results of Lung Function and $PD_{20}FEV_1$ in Asthmatic Subjects*

Subject	Test	Day 1	Day 2	
			Presmoke	Postsmoke
1.	FEV_1 (L)	3.63	3.55	3.55
	$\dot{V}max50$ (L/sec)	4.30	4.00	3.90
	FVC (L)	4.53	4.60	4.55
	$PD_{20}FEV_1$ (mg/ml)	.43		.72
2.	FEV_1	3.05	2.75	2.85
	$\dot{V}max50$	2.30	2.00	2.10
	FVC	4.80	4.53	4.40
	$PD_{20}FEV_1$	.027		.070
3.	FEV_1	3.05	3.10	2.95
	$\dot{V}max50$	2.95	2.70	2.50
	FVC	4.20	4.37	4.10
	$PD_{20}FEV_1$	.066		.120
4.	FEV_1	4.05	4.05	4.08
	$\dot{V}max50$	3.60	3.40	3.60
	FVC	5.55	5.65	5.63
	$PD_{20}FEV_1$	.260		.720
5.	FEV_1	3.30	3.10	3.13
	$\dot{V}max50$	3.35	2.70	2.90
	FVC	4.45	4.38	4.30
	$PD_{20}FEV_1$	.675		1.72
6.	FEV_1	4.10	4.50	4.40
	$\dot{V}max50$	5.30	5.00	4.60
	FVC	4.73	5.15	5.10
	$PD_{20}FEV_1$	.34		.21
7.	FEV_1	4.15	4.33	4.23
	$\dot{V}max50$	4.80	5.30	5.20
	FVC	5.05	5.20	5.10
	$PD_{20}FEV_1$	.37		3.45
8.	FEV_1	2.70	3.05	3.00
	$\dot{V}max50$	2.60	3.60	3.40
	FVC	3.63	3.75	3.75
	$PD_{20}FEV_1$	.037		.073
9.	FEV_1	2.90	2.90	2.90
	$\dot{V}max50$	2.00	2.40	2.60
	FVC	4.20	4.25	4.15
	$PD_{20}FEV_1$	.040		.047

Statistical analyses of spirometric values, carboxyhemoglobin levels, and the $PD_{20}FEV_1$ (transformed to log units as is customary) were performed with the paired Student's *t*-test. The nonparametric signed rank test was used to also evaluate changes in $PD_{20}FEV_1$ assessed without prior transformation to log units.

Results

Results obtained in individual subjects are shown in Table 2. Mean data and statistical comparisons between groups of paired data are provided in Table 3.

Symptoms and Signs

Marked eye irritation was a universal finding. Most individuals opted to wear the protective goggles after spending several minutes in the chamber. Three subjects experienced mild, transient, self-limiting cough. Except for eye and nasopharyngeal irritation, the

Table 3—*Mean Results of Lung Function, Carboxyhemoglobin Levels, and $PD_{20}FEV_1$*

	Day 1	Day 2		
	Baseline	Presmoke	Postsmoke	
FEV_1 (L)	3.43 ± .57	3.48 ± .65	3.45 ± .63	
Vmax50 (L/sec)	3.46 ± 1.14	3.46 ± 1.14	3.42 ± 1.02	
FVC (L)	4.57 ± 0.55	4.65 ± 0.58*	4.56 ± 0.60*	*p = 0.01
COHb (%)		1.71 ± 0.89	2.57 ± 1.05	p = 0.001
$PD_{20}FEV_1$ (mg/ml)	0.25 ± 0.22		0.79 ± 1.13	p = 0.043
log $PD_{20}FEV_1$	−1.92 ± 1.23		−1.21 ± 1.54	p = 0.022

*Data expressed as mean ± SD.

subjects were comfortable and spent the time in the chamber reading or studying. No subject complained of headache, chest pain, or abdominal pain. No subject had wheezes detectable by auscultation either immediately before or after the period of involuntary smoking.

Blood Carboxyhemoglobin Analysis

The pre-exposure venous blood carboxyhemoglobin (COHb) level was 1.71 ± 0.89 percent (mean ± SD). Following passive smoking, the COHb level was 2.57 ± 1.05 ($p<0.001$). This represents an increase in the mean COHb level of 0.86. This is in close agreement with the expected increase in COHb content following exposure to 40 to 50 ppm carbon monoxide for 60 minutes.[24-28]

Lung Function

Results of baseline lung function on day 1 were normal in four subjects, showed small airways obstruction in another four subjects, and revealed mild airways obstruction (FEV_1 between 65 percent and 80 percent of predicted) in one subject. There was no difference between day 1 baseline lung function and day 2 pre-smoke lung function. Comparison of day 2 presmoke lung function and postsmoke lung function showed no difference in FEV_1 or Vmax50. The FVC showed a small decrease (2 percent) following passive smoking ($p = 0.01$).

Airway Reactivity

The baseline $PD_{20}FEV_1$ on day 1 showed that each subject had a high degree of nonspecific bronchial responsiveness compared to a normal population

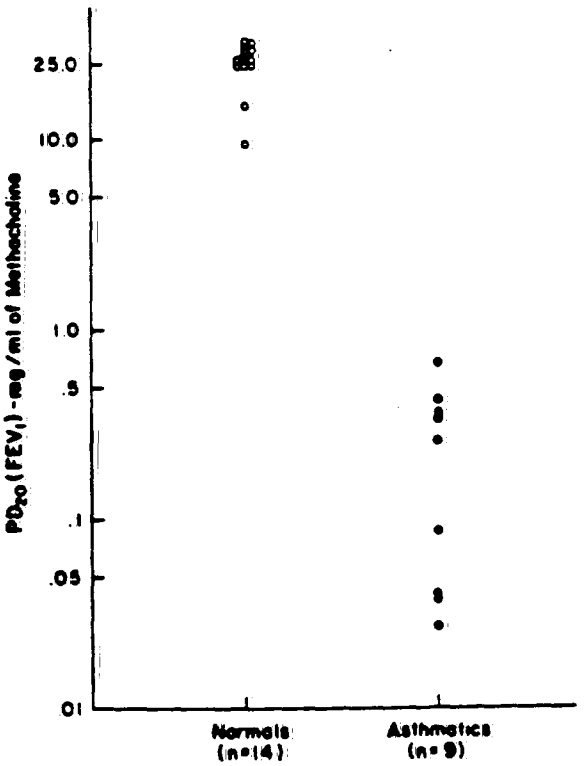

FIGURE 1. The methacholine responsiveness of the study population is compared with individuals who gave no history of asthma. The asthmatic subjects have a very low $PD_{20}FEV_1$, indicating a high degree of airway reactivity.

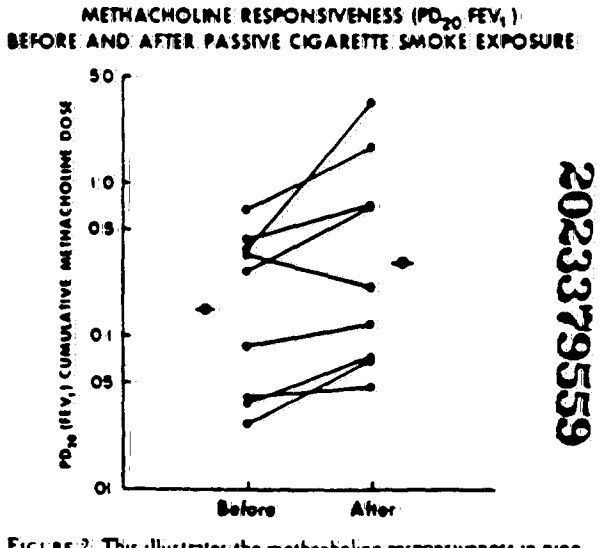

FIGURE 2. This illustrates the methacholine responsiveness in nine stable asthmatics before and after passive smoking. Exposure to cigarette smoke resulted in an increased $PD_{20}FEV_1$, indicating a decrease in airway reactivity ($p = 0.022$). The mean values are also illustrated (antilog of the mean of the log $PD_{20}FEV_1$ values).

tested in our laboratory (Fig 1). This is to be expected but confirms that our subjects, who were asymptomatic at the time of testing, are asthmatics.

A comparison of baseline $PD_{20}FEV_1$ on day 1 with postexposure day 2 is provided in Figure 2. Eight of the nine subjects showed an *increase* in $PD_{20}FEV_1$. The mean $PD_{20}FEV_1$ before smoke was .25 ± .22 mg/ml and after exposure was .79 ± 1.13 mg/ml ($p = 0.04$) while the log $PD_{20}FEV_1$ increased from −1.92 to −1.21 ($p = 0.02$).

Discussion

Involuntary smoking produces unpleasant symptoms in many individuals.[1,2,17] These subjective complaints may be sufficient cause to regulate smoking in confined public places. However, it remains controversial whether acute passive smoking is associated with important pulmonary physiologic hazards. The present study was designed to investigate whether involuntary smoking presents an acute respiratory risk to asymptomatic asthmatic individuals.

Our data demonstrate that one hour of passive cigarette smoke inhalation by young, clinically stable asthmatics produced no change in maximal expiratory flow rates. Furthermore, passive smoking caused a slight *decrease* in nonspecific bronchial reactivity assessed via methacholine bronchoprovocation. Our subjects were exposed to a severe simulation of passive smoking, beyond what normally occurs in the majority of social or occupational environments.[17] A carbon monoxide level in the ambient air of 40 to 50 ppm far exceeds the level found in office environments where smoking is permitted and is higher than the peak hourly averages usually found in taverns or nightclubs.[17] Blood carboxyhemoglobin determinations confirmed the degree of passive smoke inhalation by our subjects.

Two previous studies[19,20] investigated the effect of passive smoking on lung function in asthmatics, however, neither evaluated the influence of such involuntary smoking on airway reactivity. Shephard et al[20] studied 14 asthmatic subjects and found that the FEV_1 and $\dot{V}max50$ were unchanged after passive smoking. In their study, the intensity of exposure was less (carbon monoxide level in chamber was about 24 ppm), but the duration was longer (two hours). Their subjects were older than ours. Furthermore, the baseline pulmonary function of their subjects demonstrated airflow obstruction ($FEV_1 = 68 \pm 19$ percent of predicted, range 30 percent to 91 percent) and several of the subjects were receiving oral asthma medications. Additionally, four of their subjects gave a specific history of "exacerbation" with exposure to cigarette smoke, nevertheless, this subgroup also experienced no decrement in pulmonary function. In contrast to our results and those of Shephard et al,[20] Dahms et al[19] demonstrated a 20 percent decrease in FEV_1 and FVC following passive smoking in ten patients with bronchial asthma. It is difficult to account for the different results based upon experiment design or patient selection, although such factors may have played a role. In Dahm's study, the smoke exposure was less intense (one hour of a calculated carbon dioxide concentration of 15 to 20 ppm; the average increase in COHb level during exposure was 0.40). Their patients were young (age 18 to 26 years), and baseline lung function demonstrated only mild impairment; the mean FVC was 79.2 percent of predicted and the mean FEV_1 was 73.7 percent of predicted. The subjects continued taking medications (except bronchodilators beginning four hours prior to exposure), but the authors did not describe what medications were taken and how many subjects were on medications. However, one-half of their subjects were included because of a history of specific complaints when exposed to cigarette smoke, only the remaining five were recruited at random. In short, our study is in agreement with Shephard et al[20] and acute at variance with Dahms et al[19] regarding the effect of passive smoking on maximal expiratory flow in asthmatics. The present study additionally investigated the effect of passive smoking on bronchial reactivity.

The finding that passive smoking caused a *decrease* in nonspecific airway responsiveness (increased $PD_{20}FEV_1$) was unexpected. The clinical significance of the change is uncertain, since the magnitude was small. Only one subject had a change in $PD_{20}FEV_1$ of at least one log dose (tenfold shift), an increment that is considered clinically important.[6] It is not known whether lesser changes in $PD_{20}FEV_1$ are important. Although our data show that passive smoking caused a small decrease in airway reactivity, the possibility that this could be associated with an amelioration of the underlying asthma cannot be determined from our study.

The reduction in nonspecific airway responsiveness that we observed might have been mediated by pharmacologically active substances present in cigarette smoke. Inhalation of cigarette smoke causes increased plasma levels of the sympathetic neurotransmitter norepinephrine as well as the adrenomedullary hormone epinephrine.[29] It is possible that catecholamines released locally from sympathetic nerve ganglia, or into the circulation from the adrenal glands, may modify airway smooth muscle reactions. Catecholamine release in response to tobacco smoke inhalation is probably mediated by nicotine. Increased blood and urinary nicotine levels are found in people with mild to moderate passive smoking exposures.[29,30] Wallis et al[31] have demonstrated that inhalation of nicotine diminished airway responsiveness to methacholine in baboons who were highly reactive to methacholine, even

though nicotine inhalation had no direct bronchodilator effect on lung function.

Quantification of bronchial responsiveness may be affected by the prechallenge airway caliber.[32,33] This might be due to altered distribution of inhaled aerosol particles, such that a greater portion may deposit on the segmental airways, a site where constriction has a profound effect on the FEV_1. Furthermore, the exponential relationship between airway diameter and resistance to airflow may mean that an equivalent amount of airway narrowing may cause a much greater decrement in FEV_1 in a patient who started the challenge test with constricted airways. Since the lung function of our subjects was the same prior to each of the two methacholine tests, the influence of baseline airway caliber probably was not important in our results.

The FEV_1 test requires a forced vital capacity maneuver following inspiration to total lung capacity. Full lung inflation can reduce or abolish bronchoconstriction induced by pharmacologic agents in healthy subjects.[6] Thus, detecting slight airway responses to inhaled agents in healthy nonasthmatic subjects requires the use of lung function tests that do not involve inspiration to total lung capacity. In such cases, partial expiratory flow volume curve initiated from end-tidal inspiration, or plethysmographic measurements of airway resistance (SGaw) can be utilized. However, in asthmatics, reduction of bronchomotor tone by lung inflation is minimal or absent, and therefore, the FEV_1 is a useful and reliable test for assessing bronchial reactivity in such patients.[9,10] Furthermore, SGaw may be influenced by suggestion, whereas FEV_1 generally is not.[34,35] This may be due to vagal pathways causing subtle changes in large airway tone. Eliminating the effect of suggestion is important in this study, where the subject cannot be "blinded" to the presence of cigarette smoke. And finally, the $PD_{35}FEV_1$ shows less day-to-day variability than $PD_{35}SGaw$ and may be a better test to use when comparing bronchoprovocation tests performed on different days.[9]

We emphasize that this study did not evaluate several aspects that may be relevant to the "real life" problem of passive smoking by asthmatics. Our investigation evaluated only the immediate effects of a one-hour period of involuntary smoking. We did not test whether delayed effects of an acute exposure may occur. Furthermore, our subjects had virtually normal lung function during the study and the findings might be different for asthmatics exposed to cigarette smoke during an episode of bronchospasm. Not to be overlooked is the possible effect of chronic passive smoking. Chronic cigarette smoking may lead to increased airway reactivity in normal subjects.[36-38] By analogy, chronic involuntary smoking might lead to clinical deterioration in asthmatics. Also, the development or severity of asthma in children may be influenced by parental smoking.[39,40] And, finally, there may be a subset of asthmatics with a specific allergy to constituents of tobacco smoke.[41,42] Further work will be required to elucidate whether passive cigarette smoking represents a risk to such individuals. Nevertheless, the current study suggests that passive cigarette smoking presents no acute respiratory risk to young asymptomatic asthmatics.

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